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**EUROPEAN PATENT APPLICATION**

⑰ Application number: 88110950.8

⑤① Int. Cl.<sup>4</sup>: **A61K 6/06** , **A61L 27/00** ,  
**A61K 6/08**

⑱ Date of filing: 08.07.88

③③ Priority: 10.07.87 JP 172445/87  
10.07.87 JP 172446/87  
13.10.87 JP 257939/87  
13.10.87 JP 257940/87  
10.06.88 JP 143122/88

④③ Date of publication of application:  
11.01.89 Bulletin 89/02

⑥④ Designated Contracting States:  
**DE FR GB**

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⑤④ **Composition for forming calcium phosphate type hardening material and process for producing such hardening material.**

⑤⑦ A composition for forming a calcium phosphate type hardening material comprising (1) powder comprising at least one of  $\alpha$ -tricalcium phosphate and tetracalcium phosphate, (2) an acidic aqueous solution, and (3) a polysaccharide.

**EP 0 298 501 A2**

## COMPOSITION FOR FORMING CALCIUM PHOSPHATE TYPE HARDENING MATERIAL AND PROCESS FOR PRODUCING SUCH HARDENING MATERIAL

### FIELD OF THE INVENTION

5 The present invention relates to a composition for forming calcium phosphate type hardening material and a process for producing such a hardening material. More particularly, the present invention relates to a composition for forming a calcium phosphate type hardening material which is useful as a medical or dental cement material or a bone prosthetic material. The present invention also relates to a process for producing a hardening material in block form or other hardening materials useful as artificial bones and dental roots.

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### BACKGROUND OF THE INVENTION

15 Calcium phosphate compounds, in particular hydroxyapatite, have an excellent biocompatibility and their use as biomaterials in medical or dental fields has been widely investigated.

Calcium phosphate compounds other than apatite are known to be converted to hydroxyapatite upon hydrolysis, and it has recently been found that the hydroxyapatite so produced can be hardened under certain conditions. In an attempt to exploit this phenomenon, several efforts have been made to use calcium phosphate powders as dental or medical cement materials (as described, for example, Japanese Patent Application (OPI) Nos. 12705/87, 161206/87, 182263/84 and 88351/84) (the term "OPI" as used herein means an unexamined published Japanese patent application)

20 Calcium phosphate type hardening materials are currently made from three types of calcium phosphate, i.e.,  $\alpha$ -tricalcium phosphate ( $\text{Ca}_3(\text{PO}_4)_2$ ), tetracalcium phosphate ( $\text{Ca}_4(\text{PO}_4)_2$ ), and mixtures of these two compounds. In order to prepare  $\alpha$ -tricalcium phosphate, calcium carbonate is mixed with calcium pyrophosphate and the mixture is calcined at  $1,250^\circ\text{C}$ . To prepare tetracalcium phosphate, calcium carbonate and calcium pyrophosphate are finely ground and mixed, followed by the mixture being calcined at  $1,500^\circ\text{C}$ . A mixture of  $\alpha$ -tricalcium phosphate and tetracalcium phosphate is prepared by finely grinding and mixing the respective ingredients prepared by the above-described methods.

30 Since these methods involve a solid phase reaction, the powders obtained lack uniformity in composition. With such powders, a hardening reaction therefore does not proceed uniformly and this results in a hardening material having a reduced strength. Furthermore, because of the high firing temperatures employed, the powders prepared by these conventional methods have low activity and suffer from such disadvantages as a prolonged hardening time and a decrease in the strength of the resulting hardening materials on account of incomplete hardening.

35 Calcium phosphate powders are hardened by mixing them with a hardening solution. In order to ensure that the hardening material will do no harm to body tissues, it is desirable for the mixture to have a low pH and that the hardening reaction will proceed in the neutral range. An aqueous solution of citric acid has heretofore been considered the best hardening solution capable of satisfying these requirements. However, 40 such an aqueous solution of citric acid still leaves room for improvement, especially when compared with acrylic cement materials which have been commonly used in the art. The considerable problem is that a mixture of a calcium phosphate powder and an aqueous citric acid solution is not highly plastic and cannot be readily formed into a desired shape.

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### SUMMARY OF THE INVENTION

50 An object of the invention is to provide an improved composition for forming a calcium phosphate type hardening material. This composition employs a powder component which can be produced by any suitable method, allows a hardening reaction to proceed uniformly and thoroughly in the neutral range, can be readily shaped into a desired form by kneading operations, and produces a hardening material which has high strength and yet does not harm body tissues.

Another object of the present invention is to provide a process for producing such a calcium phosphate

type hardening material.

Other objects and effects of the present invention will be apparent from the following description.

As a result of various studies conducted in order to solve the aforementioned problems of the prior art, the present inventors have found that a mixture having good formability could be made from an  $\alpha$ -tricalcium phosphate and/or tetracalcium phosphate powder by using an aqueous acidic hardening solution containing a polysaccharide as a hardening solution. The present inventors also found that a hardened material of good quality could be produced from such a mixture. The present invention has been accomplished on the basis of these findings.

The present invention provides, in one aspect, a composition for forming a calcium phosphate type hardening material comprising (1) a powder comprising at least one of  $\alpha$ -tricalcium phosphate and tetracalcium phosphate, (2) an acidic aqueous solution, and (3) a polysaccharide which is preferably dissolved in the acidic aqueous solution.

In another aspect, the present invention provides a process for producing a calcium phosphate type hardening material by mixing the powder (1) with the aqueous acidic solution (2).

#### BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 is a X-ray diffraction scan of the hydroxyapatite synthesized in Example 19; and

Fig. 2 is a X-ray diffraction scan of the powder prepared in Example 19 in accordance with the present invention.

#### DETAILED DESCRIPTION OF THE INVENTION

In the present invention,  $\alpha$ -tricalcium phosphate, tetracalcium phosphate or a mixture thereof is used as a powder component. Synthesis of  $\alpha$ -tricalcium phosphate can be made by a known dry or wet process. Tetracalcium phosphate can be prepared by a known dry process involving the reaction between calcium pyrophosphate and calcium carbonate. The powder components prepared need not be completely pure and they may contain minor amounts of impurities which are generated during the synthesis. If a mixture of  $\alpha$ -tricalcium phosphate and tetracalcium phosphate is used, their proportions are not limited to any particular values, and the two compounds may be synthesized separately and thereafter mixed in appropriate proportions.

A mixture of  $\alpha$ -tricalcium phosphate and tetracalcium phosphate which is preferably used in the present invention can be prepared by the step of calcining, at a temperature of from about 1,150° C to 1,450° C under reduced pressure, a hydroxyapatite having a molar ratio of Ca/P of about 1.8 or less and more than 1.5 so as to produce a mixture of  $\alpha$ -tricalcium phosphate and tetracalcium phosphate.

In this method for producing the mixture using a reduced pressure, the hydroxyapatite having a molar ratio of Ca/P of more than 1.5 but not exceeding about 1.8 can be readily synthesized by a wet method. If such hydroxyapatite is calcined under reduced pressure at about 1,150° C or more, it is thermally decomposed to form  $\alpha$ -tricalcium phosphate and tetracalcium phosphate in admixture. The resulting mixture is uniform in composition. Hydroxyapatite generally starts to be thermally decomposed at a temperature near 1,400° C if the pressure is atmospheric. In the method described above, the pressure is subatmospheric, so the reaction of thermal decomposition is allowed to proceed at a fairly high speed even at the comparatively low temperature of about 1,150° C. This is beneficial to the purpose of simplifying the manufacturing steps and reducing the production cost. The low calcining temperature offers the additional advantage of providing a highly active powder for use as a component in calcium phosphate type hardening materials.

The hydroxyapatite used as the starting material in the method described above can be readily synthesized by a wet process in which an aqueous solution of phosphoric acid is reacted with a suspension of calcium hydroxide by a known method. The molar ratio of Ca/P of this hydroxyapatite must be more than 1.5 and about 1.8 or less, preferably from about 1.6 to 1.8. If the molar ratio of Ca/P is 1.5, the product thus-obtained does not become a mixture but  $\alpha$ -tricalcium phosphate per se. If the molar ratio of Ca/P exceeds about 1.8, calcium oxide which is deleterious to the human body will form during calcining. The Ca/P molar ratio of the hydroxyapatite used as the starting material can be adjusted by changing the proportions of calcium hydroxide and phosphoric acid which are to be reacted in the synthesis process of

the hydroxyapatite. By changing the Ca/P molar ratio of the starting hydroxyapatite, the proportions of  $\alpha$ -tricalcium phosphate and tetracalcium phosphate to be finally produced can be adjusted to desired values.

After synthesis by a suitable method such as a wet process, the starting hydroxyapatite is preferably rendered in powder form by suitable means such as filtration, centrifugation or spray-drying. It is also preferred for the hydroxyapatite to be thoroughly dried to remove as much water as possibly by a suitable method such as precalcination at a temperature of about from 500 to 700°C before it is thermally decomposed in a subsequent calcining step.

The thus prepared hydroxyapatite is calcined under reduced pressure at a temperature of from about 1,150°C to 1,450°C. If the calcining temperature is less than about 1,150°C, the intended thermal decomposition reaction will not take place to a practically acceptable extent even if the pressure is decreased.

The reason why the hydroxyapatite is calcined under reduced pressure is that the calcining temperature can be lowered so as to simplify the manufacturing steps and to reduce the production costs, and that a product of high activity can be attained. The reduced pressure under which the hydroxyapatite is calcined is preferably about 10 Pa or less, more preferably about  $10^{-2}$  Pa or less.

The mixture of  $\alpha$ -tricalcium phosphate and tetracalcium phosphate which is prepared by thermal decomposition under reduced pressure of the hydroxyapatite having a Ca/P molar ratio of more than 1.5 but not exceeding about 1.8 can be used as a powder component of the composition of the present invention and in the process for producing a hardening material. Additionally, this mixture may be used as a powder for thermal spray as described for example, in Kinzoku Hyomen Gijuttu Binran (Handbook of Metal Surface Treating Technology), pp. 1,132 to 1,139 (Nikkan Kogyo Shinbunsha, 1963) and Japanese Patent Application (OPI) No. 65871/88. If desired, the powder of the mixture may be granulated and fired at a temperature not higher than the point where conversion to hydroxyapatite takes place, thereby producing granules of bone prosthetic filler. These granules have the advantage that they can be placed at will in any areas of any shape that need prosthetic treatments. Other applications of the mixture include use as a column packing similar to the case of the hydroxyapatite.

The aqueous acidic solution for use as a hardening solution in the present invention may contain various inorganic and organic acids dissolved therein. Examples thereof include inorganic acids such as phosphoric acid, and organic acids such as acetic acid, lactic acid, citric acid, malic acid, malonic acid, succinic acid, glutaric acid, tartaric acid and polyacrylic acid. In the present invention, these acids are used in aqueous solution having acid concentrations which are preferably about 25 wt% or more, more preferably from about 25 to 55 wt%. If the acid concentration of the aqueous acidic solution is less than about 25 wt%, the hardening material obtained by mixing it with the powder component will not exhibit the desired strength.

In accordance with the present invention, polysaccharides are added and dissolved in the various aqueous acidic solutions described above. Any polysaccharides can be used if they are soluble in the solution and will not harm body tissues. Examples thereof include chitosan and starch, with chitosan being particularly preferred. The polysaccharides are dissolved in the aqueous acidic solutions in concentrations preferably about 0.05 wt% or more. The effectiveness of the polysaccharides is not sufficient if they are added in concentrations of less than about 0.05wt%.

By using the polysaccharide-containing aqueous acidic solutions as hardening solutions, the  $\alpha$ -tricalcium phosphate and/or tetracalcium phosphate as the powder component can be hardened mildly in the neutral range, and the composition for forming hardening materials is plastic enough to be readily formed into any complex shape.

The hardening reaction can be allowed to proceed even more mildly by further adding and dissolving at least one of glycerin, a monosaccharide, an oligosaccharide and a sugaralcohol in the aqueous acidic solution as the hardening solution having a polysaccharide dissolved therein. Examples of the monosaccharide include glucose and fructose, which may be used either alone or in admixture. Examples of the oligosaccharide include saccharose, maltose, lactose and raffinose, which may be used either alone or in admixture. Examples of the sugaralcohol include sorbitol, mannitol and xylitol, which may also be used either alone or in combination. Glycerin, monosaccharides, oligasaccharides and sugaralcohols may be used either independently or in combination.

When one or more of glycerin, monosaccharides, oligosaccharides and sugaralcohols are used, the total concentration thereof is preferably about 40 wt% or less, more preferably from about 5 to 40 wt%. If the concentration of these additives exceeds about 40 wt%, increased difficulty will be encountered in dissolving them in the aqueous acidic solution.

In accordance with the process of the present invention, the powder component and the hardening solution prepared by the procedures described above are mixed so as to initiate the hydrolysis reaction of

5  $\alpha$ -tricalcium phosphate and/or tetracalcium phosphate, thereby producing hydroxyapatite to provide a hardening material. The powder component and the hardening solution are preferably mixed in such proportions that the ratio of the powder to the solution is within the range of from about 0.4 to 2.7 by weight more preferably from about 0.4 to 2.0 by weight. If the ratio of the powder to the solution is less than about 0.4, the solids content is too low to ensure desired strength for the hardened material. If the ratio of the powder to the solution exceeds about 2.7, it becomes difficult to attain uniform mixing of the powder and the solution.

The following examples are provided for the purpose of further illustration the present invention but are in no way to be taken as limiting. All parts, ratio and presents are by weight unless otherwise indicate.

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#### EXAMPLE 1

15 As aqueous solution of phosphoric acid was reacted with a suspension of calcium hydroxide by a conventional method. The reaction product was dried and calcined at 1,200° C to obtain  $\alpha$ -tricalcium phosphate in powder form. Two grams of this powder was mixed with 1 g of a hardening solution prepared by dissolving 0.1 g of chitosan ("Flownak N" of Kyowa Yushi Kogyo K.K.) in 10 g of an aqueous solution of 40% citric acid. A plastic gum-like composition was obtained and this composition hardened in about 7
 20 minutes to produce a hardening material having a high strength.

#### EXAMPLE 2

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An aqueous solution of phosphoric acid was reacted with a suspension of calcium hydroxide by a conventional method. The reaction product was dried and calcined at 1,200° C to obtain  $\alpha$ -tricalcium phosphate in powder form. Two grams of this powder was mixed with 1 g of a hardening solution prepared by dissolving 0.1 g of chitosan and 3 g of saccharose in 10 g of an aqueous solution of 40% citric acid. A
 30 plastic gum-like composition was obtained and this composition hardened in about 10 minutes to produce a hardening material having a high strength.

#### EXAMPLE 3

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Calcium pyrophosphate was reacted with calcium carbonate by a conventional method, and calcined to obtain tetracalcium phosphate in powder form. Two grams of this powder was mixed with 1 g of a hardening solution prepared by dissolving 0.1 g of chitosan and 3 g of saccharose in 10 g of an aqueous
 40 solution of 40% citric acid. A plastic gum-like composition was obtained and this composition hardened in about 5 minutes to produce a hardening material having a high strength.

#### EXAMPLE 4

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50  $\alpha$ -Tricalcium phosphate and tetracalcium phosphate were prepared separately by conventional methods and mixed at a weight ratio of 2/1 to make a mixed powder. Two grams of this mixed powder was mixed with 1 g of a hardening solution prepared by dissolving 0.1 g of chitosan in 10 g of an aqueous solution of 40% citric acid. A plastic gum-like composition was obtained and this composition hardened in about 5 minutes to produce a hardening material having a high strength.

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EXAMPLE 5

Two grams of the mixed powder prepared in Example 4 was mixed with 1 g of a hardening solution prepared by dissolving 0.1 g of chitosan and 3 g of saccharose in 10 g of an aqueous solution of 40% citric acid. A plastic gum-like composition was obtained and this composition hardened in about 7 minutes to produce a hardening material having a high strength.

EXAMPLE 6 TO 17

Two grams of a powder (indicated in Table 1) was mixed with 1 g of a hardening solution (indicated in Table 1). Similar to the cases of Examples 1 to 5, plastic gum-like compositions were obtained and hardening materials having a high strength could be produced from the compositions. The periods time required for these compositions to harden are also shown in Table 1, in which  $\alpha$ -TCP and COP denote  $\alpha$ -tricalcium phosphate and tetracalcium phosphate, respectively.

TABLE 1

5	Example	Powder composition	Composition of hardening solution						Time to harden (min)
			Aqueous acidic solution		Polysaccharide		Other additives		
			acid and its concentration	amount (g)				amount (g)	
10									
15	6	$\alpha$ -TCP	40% citric acid	10	chitosan	0.1	glycerin	3	10
	7	COP	40% citric acid	10	chitosan	0.1	sorbitol	3	5
	8	2:1 mixture of $\alpha$ -TCP + COP	40% citric acid	10	chitosan	0.1	glucose	3	7
20	9	$\alpha$ -TCP	40% malic acid	10	chitosan	0.1	-	-	7
	10	$\alpha$ -TCP	40% malic acid	10	chitosan	0.1	glucose	3	10
	11	COP	40% malic acid	10	chitosan	0.1	glycerin	3	5
25	12	2:1 mixture of $\alpha$ -TCP + COP	40% malic acid	10	chitosan	0.1	sorbitol	3	7
	13	COP	40% malic acid	10	chitosan	0.1	saccharose	3	5
	14	$\alpha$ -TCP	40% phosphoric acid	10	chitosan	0.1	saccharose + glycerin	3 + 3	2
30	15	COP	25% polyacrylic acid	10	chitosan	0.1	-	-	10
	16	$\alpha$ -TCP	25% polyacrylic acid	10	chitosan	0.1	glycerin	3	20
	17	2:1 mixture of $\alpha$ -TCP + COP	25% polyacrylic acid	10	chitosan	0.1	saccharose	3	15
40									

COMPARATIVE EXAMPLE 1

The same procedures as in Example 1 were repeated except that chitosan was not added to the hardening solution. The composition obtained was not plastic and had a deteriorated formability although the composition hardened in about 2 minutes.

EXAMPLE 18

An aqueous solution of phosphoric acid was reacted with a suspension of calcium hydroxide by a conventional method, and the reaction product was dried to obtain hydroxyapatite. The identity of the product was established by X-ray diffraction, the results of which are shown by an X-ray diffraction scan in Fig. 1. A chemical analysis revealed that the resulting hydroxyapatite had a Ca/P molar ratio of 1.67.

This hydroxyapatite was calcined at 1,200° C for 1 hour at a pressure of  $1.3 \times 10^{-4}$  Pa. The resulting product was analyzed by X-ray diffraction as above and the results are shown in Fig. 2. The appearance of two characteristic peaks a ( $\alpha$ -tricalcium phosphate) and b (tetracalcium phosphate) verified the production of a mixture of  $\alpha$ -tricalcium phosphate and tetracalcium phosphate by thermal decomposition of hydroxyapatite.

Three grams of this mixture in powder form was mixed with 2 g of a commercial aqueous solution of gluconic acid (product of Wako Pure Chemical Industries, Ltd.; concentration, ca. 50%). The mixture underwent a hydrolytic reaction and hardened in about 1 hour.

#### EXAMPLE 19

The powder prepared as in Example 18 was mixed with hardening solutions (indicated in Table 2) at a weight ratio of 1/1 and hardening materials were obtained. The hardening times and the temperatures produced by the exothermic reaction of the hardening process are also shown in Table 2.

TABLE 2

Composition of Hardening Solution (wt%)				Hardening time (min)	Temperature (°C)
Citric acid	Glycerin	Sorbitol	Saccharose		
45	10	0	0	0.75	55
45	20	0	0	2	51
45	30	0	0	8	45
45	0	10	0	0.8	53
45	0	20	0	2	51
45	0	0	10	1	52
45	0	0	20	2.8	49
45	0	0	0	0.5	66

#### EXAMPLE 20

The mixture of  $\alpha$ -tricalcium phosphate and tetracalcium phosphate prepared in Example 18 was used as a powder component. Two grams of this powder was mixed with 1 g of a hardening solution prepared by dissolving 0.1 g of chitosan ("Flownak N" of Kyowa Yushi Kogyo K.K.) in 10 g of an aqueous solution of 40% citric acid. A plastic gum-like composition was obtained and this composition hardened in about 2 minutes to produce a hardening material having a high strength.

#### COMPARATIVE EXAMPLE 2

The same procedures as in Example 20 were repeated except that chitosan was not added to the hardening solution. The composition obtained was not plastic and had a deteriorated formability although the composition hardened in about 2 minutes.



EXAMPLE 21

5 The mixture of  $\alpha$ -tricalcium phosphate and tetracalcium phosphate prepared in Example 18 was used as a powder component. Two grams of this powder was mixed with 1 g of a hardening solution prepared by dissolving 3 g of saccharose and 0.1 g of chitosan ("Flownak N" of Kyowa Yushi Kogyo K.K.) in 10 g of an aqueous solution of 40% citric acid. A plastic gum-like composition was obtained and this composition hardened in about 9 minutes to produce a hardening material having a high strength.

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COMPARATIVE EXAMPLE 3

15 The same procedures as in Example 21 were repeated except that chitosan was not added to the hardening solution. The composition obtained was not plastic and had a deteriorated formability although the composition hardened in about 2 minutes.

In accordance with the present invention  $\alpha$ -tricalcium phosphate and/or tetracalcium phosphate is used as a powder and mixed with a hardening solution which is an aqueous acidic solution having a polysaccharide dissolved therein. The resulting composition is highly plastic and can be readily formed into a desired  
20 shape before hardening. The hardening reaction which occurs is mild and it proceeds at a moderate rate and uniformly to produce a hardening material having a high strength and which yet will not harm body tissues.

If a mixture of  $\alpha$ -tricalcium phosphate and tetracalcium phosphate is to be used as a powder component, it can be readily prepared by calcining a hydroxyapatite with a molar ratio of Ca/P of more than  
25 1.5 and about 1.8 or less at a temperature of about from 1,150 °C to 1,450 °C under reduced pressure. In this preferred embodiment, an aqueous acidic solution containing not only a polysaccharide but also at least one of glycerin, a monosaccharide, an oligosaccharide and a sugaralcohol may be used as a hardening solution. This offers further advantage of allowing the hardening reaction to proceed more uniformly to a fuller extent at a moderate and mild rate, thereby producing a hardening material having a high strength and  
30 which yet will not harm body tissues.

Therefore, the present invention provides a composition which is useful as a medical or dental cement material or a bone prosthetic material and which, immediately before use, is rendered sufficiently plastic by mixing the powder and the hardening solution to replace missing parts of a bone or tooth, and is subsequently hardened. In addition, the present invention provides a hardened biomaterial of a desired  
35 shape such as a hardening material in block form, an artificial bone or dental root.

While the invention has been described in detail and with reference to specific examples thereof, it will be apparent to one skilled in the art that various changes and modifications can be made therein without departing from the spirit and scope thereof.

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**Claims**

1. A composition for forming a calcium phosphate type hardening material comprising (1) powder comprising at least one of  $\alpha$ -tricalcium phosphate and tetracalcium phosphate, (2) an acidic aqueous  
45 solution, and (3) a polysaccharide.

2. A composition as claimed in claim 1, wherein said polysaccharide is dissolved in said acidic aqueous solution.

3. A composition as claimed in claim 1, wherein said acidic aqueous solution is an aqueous solution of an inorganic acid or an organic acid.

4. A composition as claimed in claim 3, wherein said organic acid is selected from the group consisting of acetic acid, lactic acid, citric acid, malic acid, malonic acid, succinic acid, glutaric acid, tartaric acid, and polyacrylic acid.  
50

5. A composition as claimed in claim 1, wherein the acid concentration of said acidic aqueous solution is about 25 wt% or more.

55 6. A composition as claimed in claim 4, wherein the acid concentration of said acidic aqueous solution is from about 25 to 55 wt%.

7. A composition as claimed in claim 6, wherein said acidic aqueous solution is selected from the group consisting of a citric acid solution having an acid concentration of about 40 wt%, a malic acid solution having an acid concentration of about 40 wt%, a phosphoric acid solution having an acid concentration of about 40 wt%, and a polyacrylic acid solution having an acid concentration of about 25 wt%.

5 8. A composition as claimed in claim 1, wherein said polysaccharide is chitosan.

9. A composition as claimed in claim 2, wherein the concentration of said polysaccharide in said aqueous solution is about 0.05 wt% or more.

10. A composition as claimed in claim 1, wherein the ratio of said powder to said acidic aqueous solution is from about 0.4 to 2.7 by weight.

10 11. A composition as claimed in claim 10, wherein the ratio of said powder to said acidic aqueous solution is from about 0.4 to 2.0 by weight.

12. A composition as claimed in claim 1, wherein said powder is a mixture of  $\alpha$ -tricalcium phosphate and tetracalcium phosphate.

13. A composition as claimed in claim 12, wherein said powder is produced by the step of calcining, at a temperature of from about 1,150 °C to 1,450 °C under reduced pressure, a hydroxyapatite having a molar ratio of Ca/P of about 1.8 or less and more than 1.5.

14. A composition as claimed in claim 13, wherein said acidic aqueous solution is an aqueous solution of citric acid containing at least one of a monosaccharide, an oligosaccharide, and a sugaralcohol; and said polysaccharide is chitosan.

20 15. A composition as claimed in claim 13, wherein said hydroxyapatite has a molar ratio of Ca/P of from about 1.6 to 1.8.

16. A composition as claimed in claim 13, wherein said hydroxyapatite is calcined under a pressure of about 10 Pa or less.

25 17. A composition as claimed in claim 16, wherein said hydroxyapatite is calcined under a pressure of about  $10^{-2}$  Pa or less.

18. A composition as claimed in claim 1, wherein said acidic aqueous solution contains at least one of glycerin, a monosaccharide, an oligosaccharide, and a sugaralcohol.

30 19. A composition as claimed in claim 18, wherein the concentration of said at least one of glycerin, a monosaccharide, an oligosaccharide, and a sugaralcohol in said acidic aqueous solution is about 40 wt% or less.

20. A composition as claimed in claim 19, wherein the concentration of said at least one of glycerin, a monosaccharide, an oligosaccharide, and a sugaralcohol in said acidic aqueous solution is about from 5 to 40 wt%.

35 21. A composition as claimed in claim 20, wherein the concentration of said at least one of glycerin, a monosaccharide, an oligosaccharide, and a sugaralcohol in said acidic aqueous solution is about from 10 to 30 wt%.

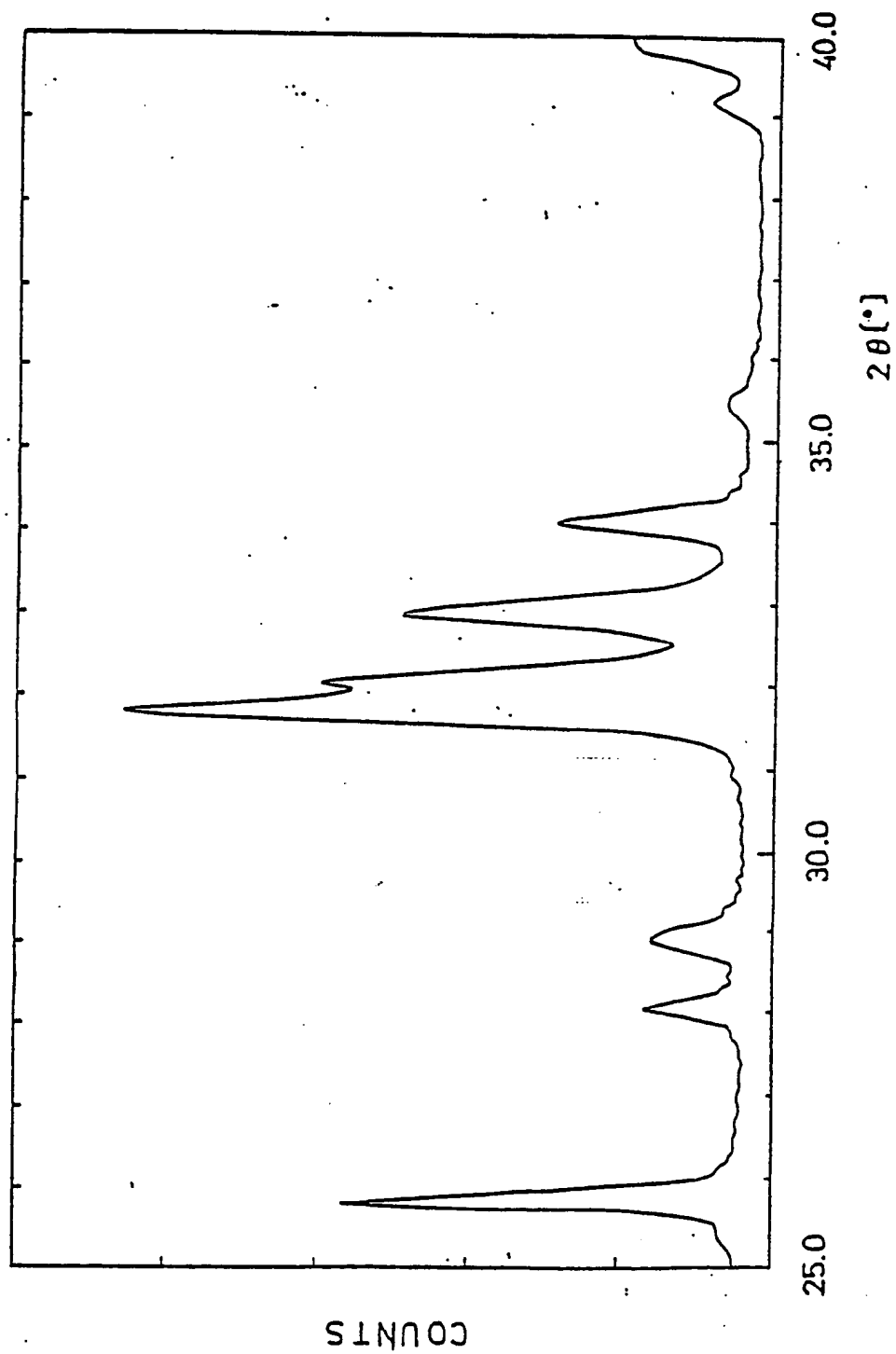
22. A process for producing a calcium phosphate type hardening material comprising the step of mixing (1) powder comprising at least one of  $\alpha$ -tricalcium phosphate and tetracalcium phosphate and (2) an acidic aqueous solution containing a polysaccharide dissolved therein.

40 23. A process for producing a calcium phosphate type powder comprising the step of calcining, at a temperature of from about 1,150 °C to 1,450 °C under reduced pressure, a hydroxyapatite having a molar ratio of Ca/P of about 1.8 or less and more than 1.5 so as to produce a mixture of  $\alpha$ -tricalcium phosphate and tetracalcium phosphate.

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Fig. 1

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**EUROPEAN PATENT APPLICATION**

21 Application number: **88110950.8**

51 Int. Cl.4: **A 61 K 6/06**  
**A 61 L 27/00, A 61 K 6/08**

22 Date of filing: **08.07.88**

30 Priority: **10.07.87 JP 172445/87**  
**10.07.87 JP 172446/87**  
**13.10.87 JP 257939/87**  
**13.10.87 JP 257940/87**  
**10.06.88 JP 143122/88**

43 Date of publication of application:  
**11.01.89 Bulletin 89/02**

64 Designated Contracting States: **DE FR GB**

88 Date of deferred publication of search report:  
**14.06.89 Bulletin 89/24**

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54 **Composition for forming calcium phosphate type hardening material and process for producing such hardening material.**

57 A composition for forming a calcium phosphate type hardening material comprising (1) powder comprising at least one of  $\alpha$ -tricalcium phosphate and tetracalcium phosphate, (2) an acidic aqueous solution, and (3) a polysaccharide.



European Patent  
Office

# EUROPEAN SEARCH REPORT

Application Number

EP 88 11 0950

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.4)
X,P	JAPANESE PATENTS GAZETTE, section Ch, week 8830, 7th September 1988, abstract no. 88-208078/30, Derwent Publications Ltd, London, GB; & JP-A-63 143 071 (M. NAGASE) 15-06-1988 * Abstract * ---	1	A 61 K 6/06 A 61 L 27/00 A 61 K 6/08
A	WO-A-8 601 113 (G. BRINKS) * Claims 3,6; page 2, lines 26-30; page 3, line 27 - page 4, line 7 * ---		
A	US-A-4 518 430 (W. BROWN) * Examples * ---		
A,D	PATENT ABSTRACTS OF JAPAN, vol. 11, no. 192 (C-429)[2639], 19th June 1987; & JP-A-62 12 705 (MEISHIN K.K.) 21-01-1987 * Whole abstract * -----		
			TECHNICAL FIELDS SEARCHED (Int. Cl.4)
			A 61 K A 61 L
The present search report has been drawn up for all claims			
Place of search THE HAGUE		Date of completion of the search 03-04-1989	Examiner COUSINS-VAN STEEN G.I.L.
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